Respiratory muscle energetics during exercise in healthy subjects and patients with COPD

Giorgio Scano\textsuperscript{a,b,*}, Michela Grazzini\textsuperscript{a,b}, Loredana Stendardi\textsuperscript{a,b}, Francesco Gigliotti\textsuperscript{a,b}

\textsuperscript{a}Department of Internal Medicine, Respiratory Disease Section, University of Florence, Italy
\textsuperscript{b}Fondazione Don C. Gnocchi, IRCCS, Pozzolatico, Florence, Italy

Received 20 September 2005; accepted 24 February 2006

Summary The energy expenditure required by the respiratory muscles during exercise is a function of their work rate, cost of breathing, and efficiency. During exercise, ventilatory requirements increase further exacerbating the potential imbalance between inspiratory muscle load and capacity. High level of exercise intensity in conjunction with contracting respiratory muscles is the reason for respiratory muscle fatigue in healthy subjects. Available evidence would suggest that fatigue of the diaphragm and other respiratory muscles is an important mechanism involved in redistribution of blood flow. Reflex mechanisms of sympathoexcitation are triggered in fatigued diaphragm during heavy exercise when cardiac output is not sufficient to adequately meet the high metabolic requirements of both respiratory and limb musculature. It is very likely that local changes in locomotor muscle blood flow may occur during exhaustive endurance exercise and that changes may have important effect on O\textsubscript{2} transport to the working locomotor muscles and, therefore, on their fatigability. In a condition when the respiratory muscles receive their share of blood flow at the expense of limb locomotor muscles, minimizing mechanical work of breathing and therefore its metabolic cost allows a greater amount of cardiac output to be available to be delivered to working limb muscles. Malfunction in any of the multiple components responsible for circulatory flow and O\textsubscript{2} delivery will limit the blood supply therefore inhibiting the supply of O\textsubscript{2} and the energy substrate to the contracting muscles. Studies are needed to overcome these limitations.

\& 2006 Elsevier Ltd. All rights reserved.

\textsuperscript{*}Presented in part to the European Respiratory Society Annual Congress, 8 September, 2004, Glasgow, UK.
\textsuperscript{*}Corresponding author. Department of Internal Medicine, Section of Clinical Immunology, Allergology and Respiratory Disease, University of Florence, Viale Morgagni 87, 50134 Firenze, Italy. Tel.: +39 055 4296 414; fax: +39 055 412867.
\textsuperscript{E-mail address: g.scano@dmi.unifi.it (G. Scano).}
Contents

Introduction .................................................................................. 1897
Mechanical work rate, energy cost of breathing, and efficiency of respiratory muscles .............. 1897
  Healthy subjects ........................................................................ 1897
  Patients with COPD ................................................................... 1899
Exercise-induced respiratory muscle fatigue ................................................................................. 1899
  Healthy subjects ........................................................................ 1899
  Do respiratory muscles fatigue during exercise in patients with COPD? ..................................... 1900
Respiratory muscle blood flow ......................................................................................................... 1900
Ventilatory-locomotor muscle blood flow competition during exercise ........................................... 1901
  Healthy subjects ........................................................................ 1901
  Patients with COPD ................................................................... 1902
Interaction between ventilatory and circulatory mechanics during exercise in COPD ..................... 1903
Summary and conclusions ................................................................................................................. 1904
References ..................................................................................... 1904

Introduction

A large body of scientific information on the respiratory muscles during exercise has been published since 1954. We present the accumulate knowledge with particular emphasis on researches published in the last 5–10 years. We updated previous treatments on traditional topics such as energetics and fatigability of the respiratory muscles, and locomotor-respiratory muscle blood flow competition. A MEDLINE search of articles published between 1954 and 2005 was undertaken. The energetics of the respiratory muscles has been approached on the interplay between the energy available for work, the work performed, and the efficiency of the respiratory system. We restricted our presentation to healthy human adults exercising at sea level and patients with COPD, a disease state that compromises the energy supply, increases the work of breathing and decreases the respiratory muscle efficiency.

We tried to answer the following question: (i) does respiratory muscle fatigue affect alveolar ventilation (VE); (ii) may work and cost of breathing of primary and accessory respiratory muscles compete with locomotor muscles to blood supply and oxygen uptake; (iii) what is the role of abnormality of O2 transport and utilization on the limitation of exercise tolerance in patients with COPD?

Mechanical work rate, energy cost of breathing, and efficiency of respiratory muscles

The energy expenditure required by the respiratory muscles during exercise depends upon exercise-induced changes in several types of mechanical work by the respiratory muscles1: (i) volume-dependent work against elastic forces in the tissue of the lung and chest wall. During heavy exercise a reduction in dynamic compliance and changes in end expiratory lung volume affect the amount of elastic work1; (ii) work to overcome inspiratory and expiratory flow resistance which rises disproportionally at very heavy work rates1; (iii) it is likely that extra work will be performed during deformation of the rib cage and abdominal walls in heavy exercise2; (iv) a small amount of work is expended to compress and expand gas during expiration and inspiration, respectively.

Healthy subjects

The work of breathing is the product of respiratory muscle pressure and lung volume. During quiet breathing through the nose, the work of breathing amounts to about 1 cal/min \[ W = 0.12 \text{ cal/l of VE}\], and the maximal potential work per breath is 24 cal/min. With increasing VE, the work of breathing increases because of the pressure–volume and pressure-flow characteristics of the respiratory system. During voluntary hyperventilation at 60–70l/min of VE, the work of breathing is 12–50 cal/min, whereas during exercise, for VE = 140 l/min, the work of breathing is 120 cal/min, i.e., four-fold lower than available maximal inspiratory power, and close to the maximal voluntary VE.4

Because the metabolism of the respiratory muscles is primarily aerobic, their rate of energy expenditure is equal to their oxygen consumption (VO2). For the same work of breathing, VO2 increases with increasing the breathing resistance and is the lowest during isocapnic hyperventilation.5 This is because of the isometric work of the
postural muscles which do not contribute to thorax expansion, and because of the work for gas compression and decompression. Separate measure of diaphragm power output (Wdi) indicates that the relationship of Wdi to VO2 with increasing breathing resistance is much lower than that for all inspiratory muscles.6 A likely explanation is that the diaphragm acts mainly as flow generator, whereas rib cage muscles and abdominal muscles develop the pressure to displace the rib cage and abdomen, respectively.7–9

A recent approach1,10 provides reasonable estimate of both ventilatory work and work expended in chest wall stabilization by the respiratory muscles during exercise. This is achieved by reproducing at rest esophageal work of breathing, pressures–time integral of the diaphragm, breathing pattern, end-expiratory lung volume and VE that they generate during moderate and maximal intensity exercise (70% and 100% VO2max, respectively). One limitation of this approach is, however, that it does not mimic the phasic activation of the respiratory muscles during exercise, nor it includes the energy expended for postural activity, and/or locomotor-related action of these muscles, e.g., increase in tonic activity of the abdominal muscles during the transition from walking to jogging.5 Another limitation is that the postural muscles, synergistic muscles and upper limb muscles which consume O2 may be used without necessarily inflating directly the thorax. All this explains the difficulty of measuring the VO2 of the respiratory muscles. Nevertheless, Aaron et al.10 showed that during moderate exercise the O2 cost per litre of VE remains fairly constant from 60 to 110 l/min of VE, averaging 1.5–2 ml VO2/l/min of VE, then it rises sharply to 3 ml VO2/l/min of VE as VE rises hence corresponding to 10–15% of total VO2 (VO2tot), i.e., 300–600 ml/min. Therefore, with incremental exercise as VE rises and O2 cost per l/min of VE increases with hyperventilation the O2 cost of breathing requires a greater proportion of the rise in VO2tot. This is likely to occur in elite athletes and older individuals because the high level of required VE causes expiratory flow limitation and puts the inspiratory muscles close to their maximal capacity for pressure generation. The study of Aaron et al.10 also shows that at maximal levels of exercise at a time when the slope of the relationship between VO2tot and work load is falling, the VO2 of the respiratory muscles rise to 35–45%VO2tot (see Table 3 in Aaron et al.10). Not in line with Otis “critical useful VE”1 (VEcrit) this increase was too small to require that all the increase in VO2tot be devoted to hyperventilation (see below). The level of VE would have had to be 2251 l/min for this critical level to be achieved. Similar data were obtained by Cibella et al.11 who calculated the O2 cost of breathing (VO2resp) according to the equation:

$$\text{VO2}_{\text{resp}} = \frac{W_{\text{rs}}}{4.825E},$$

where Wrs is the respiratory muscles power, E is the efficiency, and 4.825 is the caloric equivalent of 1 ml of oxygen. The slopes ∆Wrs/∆VE and ∆VO2resp/∆VE increased, while the slope ∆VO2tot/∆VE decreased with increasing VE, indicating that the additional energy uptake per unit increase in VE diminishes with increasing VE. When ∆VO2resp/∆VE = ∆VO2tot/∆VE any further increase in VE will result in less energy (O2) for doing useful external work because the respiratory muscles will use all the additional O2 provided by the increased VE. At sea level, VEmax did not exceed the critical VE (VEcrit) i.e., the critical value at which any increase in VE is not useful in terms of energetics because the gain of O2 is less than that required for respiratory muscle power. The opposite did occur at altitude when VEmax exceeded VECrit so that any further increase in VE did not provide oxygen available to exercising muscles unless respiratory muscles operate anaerobically. Unlike Margaria et al.12 who found VECrit being lower than VEmax in sedentary individuals the data by Cibella et al.11 are in line with those of Aaron et al.10 showing that VECrit should be higher in the fitter subject.

High levels of VO2resp may occur at relatively lower level of VE in healthy fit elderly subjects because aging reduces elastic lung recoil and therefore the flow volume loop, and because a stiffen chest wall increases VO2resp in healthy elderly at any given level of hyperpnea.13 Peak values of 15% of VO2tot represent the upper limits at maximal VO2resp.14,15 At maximal voluntary VE VO2resp amounts to 485–613 cal/min.4 Efficiency (E) is PV/VO2 (where P is pressure and V is flow). Therefore, VO2 is proportional to P when V is constant; the increase in V should be associated with proportional increase in E. Efficiency is greatest at 20% velocity of shortening, thereafter it decreases.16 Efficiency depends on the specific type of work. The efficiency is optimized if fast contracting muscle fibers contract rapidly against light load. In contrast, slow contracting muscles are more efficient when they develop tension. In general, respiratory muscles are rather fast muscles that reduce efficiency when they are required to contract slowly against resistive heavy work. Cala et al.17 showed that for the same work rate and pressure–time product the VO2 against
respiratory muscles. It was suggested that the O2 cost of increased VE that these patients are able to achieve during voluntary hyperventilation because of low efficiency.20,21

Patients with COPD

Because COPD increases several types of mechanical work of the respiratory muscles, their rate of work is 10–12 times greater than in healthy subjects at rest and even greater at low level of voluntary hyperventilation. Between 20 and 301/min of VE, the respiratory power output is between 20 and 40 kg m/min in COPD. At that power output, VE is 120–160 l/min in healthy subjects. Efficiency progressively decreases being higher at 20–40 l/min of VE than at 100–180 l/min of VE. VO2resp increases remarkably and steeply during the modest increase in VE that these patients are able to achieve during voluntary hyperventilation because of low efficiency.20,21

Early reports on ventilatory cost of exercise in COPD patients showed similar increase in VO2 and disproportionately greater increase in VE compared to controls for a given work load, indicating a higher O2 cost of breathing in patients.21 Because of the high VO2resp (35–40% of VO2tot) less O2 was available for the non-respiratory muscles. It was suggested that the O2 cost of increased VE during exercise could be an important factor limiting the physical performance of patients with COPD.23

An elevated VO2resp may reflect increased work of breathing as well as a decreased efficiency of the respiratory muscles; therefore it has been postulated22 that the decrease in inspiratory effort with pressure support (PS) during exercise would be associated with a corresponding reduction in O2 cost of breathing as measured by the difference in VO2 between control and PS trials. Failure to demonstrate any difference in VO2 [713(53) vs. 733(58) ml/min, respectively] was thought to be due to the fact that the anticipated reduction in the O2 cost of breathing relative to VO2tot was too small to be detected.22

Exercise-induced respiratory muscle fatigue

Healthy subjects

In this section, we update the effects of strenuous exercise on the respiratory muscles. We will not consider the global inspiratory muscle fatigue induced by breathing against a high inspiratory resistance during exercise. With regard to this topic, in an elegant paper Sliwinska et al.23 showed alteration in breathing pattern accompanied by a substantial different pattern of respiratory muscle activity. There appear to be two general causes of diaphragmatic fatigue induced by endurance exercise namely, one cause attributable to the force production by the diaphragm it self and a second due to the effects of whole body exercise per se. Johnson et al.24 were the first to demonstrate objectively that the diaphragm muscle is susceptible to exercise-induced low-frequency fatigue, especially when exercise intensity progressed beyond 85% of VO2max and was of endurance type. This study showed that diaphragmatic force output, and exercise intensity were likely factors contributing to the fatigue. Babcock et al.25 examined the role that diaphragmatic pressure generation played in the fatigue process independent of the whole body exercise effect. The effect of voluntarily mimicking at rest the diaphragm power output (509 ± 81 cm H2O/min, threshold) for a similar time period that subjects achieved during exercise at 86–93% VO2max did not result in fatigue of the diaphragm. By contrast, diaphragmatic power output in excess of the threshold did result in fatigue: as shown by a significant fall in diaphragmatic power output to bilateral phrenic nerve stimulation (BPNS). Thus, the available data show: (i) a substantial influence of endurance exercise on diaphragm fatigue; (ii) a significant reduction of the amount of diaphragm force output required to cause fatigue during endurance exercise; and (iii) on the other hand, the effect of whole body endurance exercise per se did not elicit fatigue in non-exercising muscle of the hand. It has been therefore postulated that acidification of the diaphragm via uptake of circulating lactate in conjunction with a contracting diaphragm accounted for most of the exercise-induced diaphragm fatigue. A major contribution of diaphragm work per se to exercise-induced diaphragm fatigue would be expected to occur only at high levels of metabolic requirement during which diaphragmatic pressure generation exceeds this fatigue threshold. In a second study Babcock et al.26 unloaded partially the diaphragm via...
pressure assist ventilation (PAV). PAV reduced work of breathing by 40–50% and VO₂tot by 10–15% below control, and prevented diaphragm fatigue at all BPNS frequencies and time points post exercise. These findings are consistent with the notion that the workload endured by the diaphragm is a critical determinant of exercise-induced diaphragm fatigue. Thus, while the force output of the diaphragm experienced during exercise was not sufficient to cause fatigue in the absence of locomotor muscle force output, it was critical to the development of diaphragmatic fatigue in the presence of whole body exercise. Available evidence would suggest that fatigue of the diaphragm and other respiratory muscles is an important mechanism involved in redistribution of blood flow. Development of diaphragm fatigue during exercise is a function of the relationship between the magnitude of the diaphragm work and the adequacy of its blood supply: the less the blood flow available, the less the diaphragm work required to produce fatigue. Imbalance of muscle force output vs. blood flow and/or oxygen transport availability to the diaphragm which favors fatigue appears to occur during exhaustive endurance exercise only when either the relative intensity of the exercise exceeds 85% VO₂max or arterial hypoxemia is present.

Do respiratory muscles fatigue during exercise in patients with COPD?

The inspiratory muscles are faced with an increased load in patients with COPD. During exercise the ventilatory requirement increases further exacerbating the potential imbalance between inspiratory muscle load and capacity. For these reasons patients with COPD may be particularly prone to the development of inspiratory muscle fatigue during exercise. Evidence of overt central or contractile fatigue of the diaphragm, however, has not been provided. Mador et al. studied COPD patients who exercised maximally relative to their capacity of reaching a VO₂ greater than peak VO₂ obtained during a preliminary maximal incremental cycle exercise test. Transdiaphragmatic twitch pressure (Pdiw) measured after exercise was not significantly different from baseline at any time point post exercise (10, 30 and 60 min). In two patients Pdiw had a persistent >10% fall post exercise potentially indicative of contractile fatigue of the diaphragm. The study also shows that, despite a significant increase in blood lactate post exercise, the majority of patients did not develop fatigue of the diaphragm. The authors concluded that the diaphragm adapts to chronic loading and that the degree of adaptation correlates with the severity of COPD. According to Levine et al. these adaptations include larger proportion of type I fiber, lesser proportion of type IIa and the same proportion of type IIb fibers in the costal diaphragm of patients compared to controls. Each fiber type had also higher succinate dehydrogenase activity and mitochondrial oxidative capacity leading to increased aerobic ATP generating capacity. In a further paper Levine et al. found that type I fibers generated lower force than did type II fibers. They also found an exponential relationship between the proportion of type I fibers and FEV₁ accounting for discrepancies with observations that the diaphragm of subjects with less severe COPD did not differ from those of controls with respect to the proportion of type I fibers. These authors believe that fiber type adaptations found in the diaphragm of COPD patients may represent an example of fast to slow fiber type transformation elicited by long-term respiratory muscles loading. It is the authors’ hypothesis that this diaphragm remodeling associated with COPD is characterized by trade-off of decreases in force generating capacity for increase in fatigue resistance.

Respiratory muscle blood flow

Rochester and Bettini assessed respiratory muscles blood flow by application of the Fick principle

\[ \text{VO}_2 = Q(\text{Ca}\!-\!\text{Cv})\text{O}_2, \]

where \( Q \) is blood flow and \((\text{Ca}\!-\!\text{Cv})\text{O}_2\) is the arteriovenous oxygen content difference. They showed in anesthetized dogs that inspiring through an inspiratory resistance led to much bigger increase in diaphragm VO₂ than that occurring during unobstructed hyperventilation. Furthermore, diaphragm VO₂ was linearly related to diaphragm inspiratory pressure-time index and to diaphragm electrical activity. At the highest level of effort, diaphragm O₂ requirements were met by increasing diaphragm blood flow, but diaphragm O₂ extraction plateaued. This and other studies have shown that the pattern of contraction is a major determinant of diaphragm blood flow which is in fact linked to the level of respiratory muscle activity. Negative pleural pressure holds the vessels open, whereas abdominal positive pressure compresses intramuscular vessels (increase in vascular resistance) thereby producing an effect of Starling resistance. Metabolic and neural factors, and autoregulation are also involved on
blood perfusion of the respiratory muscles such as the diaphragm.\(^6,^{36-38}\)

In experimental animals, respiratory muscle blood flow is measurable and since muscle VO\(_2\) and cardiac output usually change together a good estimate of O\(_2\) requirement can be derived from blood flow measurements. In dog whose total mass of the respiratory muscles is 5–6% of total body weight the highest diaphragm blood flow is about 265 ml/100 g/min,\(^6,^{35,39}\) and in pony a similar increase in perfusion of the diaphragm and rib cage muscles often approximate the perfusion of locomotor muscles during maximal exercise.\(^40\) In a 70 kg man respiratory total muscle mass would correspond to 3–5 kg, but total blood flow to the respiratory muscles remains to be defined.

Sexton and Poole\(^{41}\) reported that emphysema increases blood flow in the diaphragm, intercostal and abdominal muscles of exercising hamster, supporting the contention that emphysema increases the energetic requirements of the diaphragm. Diaphragm blood flow, however, was far below that found in hind limbs skeletal muscles. Whether this reflects the presence of blood flow limitation in respiratory muscles, or alternatively a blood flow reserve in the locomotor muscle or a regulatory effect remained to be defined.

In patients with emphysema the strength of contraction may limit further increase in perfusion.\(^5\) Estimate of blood flow of the respiratory muscles, based on the Fick principle, in patients is prevented by lack of data on O\(_2\) extraction ratio \([O_2\text{ER}: (CaO_2 – CVO_2)/CaO_2]\). The question whether in COPD patients O\(_2\)ER of the respiratory muscles is constant during exercise as in skeletal limb muscles\(^42\) is far from being answered.

Ventilatory-locomotor muscle blood flow competition during exercise

Healthy subjects

The hypothesis has recently been put forward that the metabolic cost of breathing required by respiratory muscles and stabilizing muscles of the chest wall limit the blood flow available for the locomotor muscles, thereby limiting their power output.\(^{43}\) By using thermo-dilution technique to study leg blood perfusion,\(^{44}\) Harms et al.\(^{43}\) have shown in elite athletes during control maximal exercise (VO\(_2\) 85–90% pred: 55–74 ml/kg/min) and exercise with inspiratory muscle work, either reduced via PAV, or increased via graded resistive loads, an inverse relationship between work of breathing on the one hand, and leg blood flow and VO\(_2\)legs % control on the other. With respiratory unloading, while VO\(_2\)tot decreased VO\(_2\)leg (%VO\(_2\)tot) increased. In that study the direct relationship of leg vascular resistance with nor-epinephrine spill over implied an increased muscle sympathetic nerve activity and vasoconstriction with respiratory muscles loading and vasodilatation with unloading. In a further study Harms et al.\(^{45}\) found that with respiratory muscles loading, total blood flow did not change while leg blood flow decreased from 77% to 71% as did VO\(_2\) secondary to increase in leg vascular resistance.\(^{45}\) In contrast, with respiratory unloading leg blood flow (85%) and leg VO\(_2\) (87%) increased in concomitance with decrease in leg vascular resistance. Blood flow of the respiratory muscles was assumed to be = 4.4L/min calculated as the difference between 26.5L/min in control and 22.3L/min by extrapolating respiratory muscles flow at zero work load. In turn, the respiratory muscles receive their share of blood flow at expense of limb locomotor muscles under condition in which total cardiac output and artero-venous O\(_2\) content difference are at maximal levels.\(^{45}\)

The influence of respiratory muscle work and leg blood flow on VO\(_2\) is trivial during submaximal exercise (50% and 75% VO\(_{2}\text{max}\)) when the 50–70% increase in work of breathing is too small to activate sympathetic vasoconstrictor efferent output because of the lack of diaphragm fatigue.\(^{46}\)

Minimizing mechanical work of breathing and therefore the metabolic cost of breathing allows for a greater share of cardiac output to be available for delivery to working limb muscles. A reduction in respiratory muscles energy stores minimizes sensory inputs and discomfort from chest wall and lung, reducing the potential for dyspnea or leg effort.\(^{47}\) Given the high demand for oxygen and blood flow by the respiratory muscles during maximal exercise, and its effect on peripheral cardiovascular system, Harms et al.\(^{47}\) hypothesized that work of breathing during strenuous exercise (90% VO\(_2\text{max}\)) would impair exercise performance. They validate their hypothesis by showing that loading the respiratory muscles resulted in curtailed performance, increased VO\(_2\), and decreased VE/VO\(_2\), whereas unloading the respiratory muscles lengthened exercise tolerance, reduced dyspnea and leg effort, and decreased VO\(_2\). The authors also argue that the fatigue of the diaphragm may have influenced its performance promoting: (i) greater use of accessory muscles that may have led to chest wall distortion; (ii) mechanical inefficiency of breathing; (iii) greater work of breathing; and (iv) increased metabolic and blood flow demand by the
It appears that respiratory muscle fatigue must occur for unloading in order to improve performance. This might explain why other studies have not found a significant effect of respiratory muscle unloading on exercise capacity.48–50

An important observation is that respiratory muscle fatigue during heavy exercise could impair limb work capacity due to blood flow redistribution even when cardiac output is not near maximal level.26 Babcock et al.26 postulated that reflex mechanisms of sympathoexcitation are triggered by metaboreceptors in the diaphragm as the muscle begins to accumulate metabolic end-products during heavy exercise when cardiac output is not sufficient to adequately meet the high metabolic requirements of both respiratory and limb musculature. To test this hypothesis St. Croix et al.51 fatigued the diaphragm by imposing high intensity contraction and high duty cycle to healthy subjects. Fatigue caused a time-dependent increase in muscle sympathetic nerve activity (MSNA) in the resting legs despite a corresponding increase in systemic blood pressure (inhibitory feedback from systemic baroreceptors are associated with increase in arterial blood pressure). MSNA was thought to be due to type IV nerve ending stimulation of the diaphragm. In a following study MSNA was found to be accompanied by significant decreases in limb vascular conductance and limb blood flow along with an increased mean arterial pressure and heart rate.52 A high MSNA has also been referred to a metaboreflex during high intensity and high frequency contractions of the expiratory muscles.53 What it still not clear is whether this metaboreflex is solely responsible for the vasoconstrictor effects of respiratory muscles on limb muscles vasculature being sufficiently powerful to override the local vasodilator effect from circulating metabolites and compromise blood flow to exercising muscles.

The appropriate exercise conditions, sufficient to elicit a significant vasoconstrictor effect from the diaphragm to the limb muscle vasculature, might also occur in chronic heart failure patients even at moderate exercise intensities of submaximal exercise when cardiac output is abnormally low,54,55 or COPD.56 In these cases respiratory muscle unloading may be especially beneficial to enhancement of exercise performance.47

To summarize, it is very likely that local changes in locomotor muscle blood flow may occur during exhaustive endurance exercise and that changes may have important effect on $O_2$ transport to the working locomotor muscles and, therefore, on their fatigability.

### Patients with COPD

Malfunction in any of the multiple components responsible for circulatory flow and $O_2$ delivery will limit the blood supply therefore inhibiting the supply of $O_2$ and the energy substrate to the contracting muscles.57 Patients with COPD characteristically show poor exercise performance indicated by a marked reduction in both peak cardiac output response, pulmonary $O_2$ uptake and work rate at peak exercise.58–60 However, the relationship between whole body $O_2$ uptake and work rate is normal and the $O_2$ uptake for a given submaximal work rate in these patients is similar to that seen in healthy sedentary subjects.61 Recently, other evidence suggests42,60,62–65 that skeletal muscle dysfunction should also be considered as playing a role in the limitation of exercise tolerance in COPD. There is also evidence that whole body fractional $O_2$ extraction may be less than normal in some patients with COPD42,60 indicating either impaired $O_2$ uptake by exercising muscles and/or abnormal redistribution of blood flow during exercise. Unlike athletes during extreme exercise,45,47 leg blood flow and leg $O_2$ delivery at a given submaximal whole-body $O_2$ uptake is normal in these patients.42,66 Finally, recent evidence demonstrates that an early increase in femoral venous blood lactate levels during exercise is not correlated with reduced $O_2$ delivery to the lower limb.42 This provides further support for a biochemical abnormality that may be considered a hallmark of muscle dysfunction in COPD.

On the other side, Macklem67 had shown the vicious circle between hyperventilation and lactic acidosis in patients with chronic heart failure and suggested that $O_2$ demands of the respiratory muscles may be a major fraction of total $O_2$ decline. In the face of hypoxemia and decreased cardiac output, the $O_2$ demand of the respiratory muscles may deprive the rest of the body of $O_2$, or alternatively the $O_2$ may be diverted from the muscles to the rest of the body.67 Furthermore, Field et al.68 showed in patients with COPD weaned from artificial VE a reduced ventilatory efficiency and increased work of breathing, which resulted in substantial increases in $V_\text{O}_{2\text{,resp}}$. In the presence of an impaired $O_2$ delivery system, the $O_2$ demands of the respiratory muscles may be excessive. As a result, “either other body tissues are robbed of much needed $O_2$ supplies, or otherwise the inspiratory muscles are deprived resulting in an inability to maintain an adequate VE”.68 Thus, competition between locomotor and ventilatory muscles for the available supplies of energy.
aggravated by inadequate cardiac pumping capacity, might limit $O_2$ supply.

The concept of respiratory-peripheral muscle competition has been bolstered by Richardson et al. in patients with severe COPD. They showed that both 100% $O_2$ and unloading of ventilatory muscles with helium increased peak work output during two-legged exercise. Oxygen, but not helium resulted in 2.2-fold increase in one-legged exercise (knee extensor muscle) specific power output (10 vs. 4 W/kg) than during whole body exercise. Improved power output with $O_2$ probably occurred because of greater blood perfusion and energy supply. The effect with helium during whole body exercise was due to unloading the respiratory muscles with fall in muscle output. Helium, however, did not improve the performance of the knee extensor muscle because of the lower level of VE in a condition where blood flow competition between the respiratory and peripheral skeletal muscles is not likely. The beneficial effect of oxygen also suggests that the respiratory system is not the sole constraint to oxygen consumption. This study provide also the evidence of a skeletal muscle metabolic reserve during whole body exercise in this population. In turn, Richardson et al. maintain that the major limitation to exercise performance in patients who exercise beyond the lactate threshold is notably an inadequate $O_2$ supply.

Simon et al. have recently reported that for a work load between 20 and 40 W, $VO_2$ leg, leg blood flow and arterio-venous $O_2$ content difference reached a plateau in one of two groups of COPD patients. Because $VO_2$ tot kept rising in both groups the relationships of $VO_2$ tot with $VO_2$ leg, leg blood flow, and arterio-venous $O_2$ content difference at peak exercise were lower in the "plateau" group. Despite similar respiratory function at baseline, greater VE, leg vascular resistance and dyspnea at submaximal exercise suggest greater mechanical respiratory constraint in the "plateau" group. Assuming that cardiac output kept rising (according to the 'Fick's principle') a competition in blood flow between peripheral and ventilatory muscles should be considered in the plateau group. In turn, competition between ventilatory and locomotor muscles for the available energy supplies increases with increasing work of breathing.

Competition is an important factor in the early appearance of anaerobic threshold and it can markedly aggravate a situation already compromised by a reduction in cardiac output and tissue perfusion at high exercise work load. Respiratory muscle stress associated with mild hypoxia or isocapnic hyperventilation causes mild increase in lactic acid (1 mmol/l). Pulmonary vascular disease that accompany COPD may decrease blood flow to exercising respiratory muscles and decrease their aerobic exercise capacity. Does this increase the contribution of the respiratory muscles to increasing blood lactate levels? Study in large animals showed that the diaphragm does not produce lactic acid during maximal exercise. In patients with COPD voluntary hyperventilation against a background of constant work load exercise at the anaerobic threshold brings VE to the same levels as during progressive exercise, but peak lactic acid only modestly increase well below the levels attained during progressive exercise. Despite the correlation between the increased level of airway obstruction and the increased level of lactate, the increased volitional VE was associated with an increase in blood lactate of only 0.5 mEq/l. This study suggests that the respiratory muscles do not importantly contribute to lactic acidosis during maximal exercise. Oelberg et al. found that lactate threshold occurred at an early (lower) $O_2$ extraction ratio in COPD patients compared with controls (<0.50 vs. 0.57, respectively), and was not influenced by unloading the ventilatory muscles whilst breathing helium. In turn, the respiratory muscles contribute to a small extent blood lactic acid production.

**Interaction between ventilatory and circulatory mechanics during exercise in COPD**

The mechanisms that couple VE to cardiac output during exercise are still not well understood. On the inspiratory side, changes in intrathoracic pressure imposed primarily at rest in supine humans are shown to exert effects on both left and the right heart. With increasing negativity of intrathoracic pressure, venous return increases (preload). Increasing intrathoracic negativity also implies an increase in transmural pressure across the left ventricle (afterload). Increases in right atrial and ventricular filling will compromise left ventricular expansion. Both will compromise left ventricular stroke volume and cardiac output. Preload effects dominate the effect of changes in intrathoracic pressure on stroke volume. Given the finding of reduced stroke volume with respiratory muscle unloading during maximal exercise, one may speculate that less negative esophageal pressure during inspiration reduces venous return thereby resulting in reduction in stroke volume and cardiac output. Furthermore, increased pulmonary vascular resistance should increase the afterload of the right ventricle. Montes de Oca et al. proposed that the large pressure
swings observed during exercise can constrain left ventricular function, thus limiting both peak cardiac output and exercise tolerance in patients with severe COPD. If the work of breathing increases, \( \text{VO}_2 \text{resp} \) increases and, beyond the anaerobic threshold, this should deprive the locomotor muscles of some of their perfusion.

On the expiratory side, the mechanics of breathing may interfere with cardiovascular function. High abdominal pressures interfere with venous return from exercising leg muscles.\(^{76-80}\) The high expiratory pleural pressure interferes with venous return to right heart, and a high alveolar pressure increases pulmonary vascular resistance and decreases both left heart filling and cardiac output.\(^{57}\) In presence of tidal flow expiratory limitation, the expiratory muscles might develop excessive pressure in the vain attempt to increase flow; above the anaerobic threshold the perfusion to the locomotor and respiratory muscles provides insufficient oxygen to meet the demands.\(^{67}\) During activity, patients with COPD are exposed to expiratory load and dynamic hyperinflation as ventilatory demand increases. These alterations can affect cardiac function. The separate influence of dynamic hyperinflation and expiratory load on cardiac output (CO) are not likely to be assessed in these patients. Data in healthy subject, however, indicate that mild to moderate expiratory load limits CO primarily through an influence on esophageal and gastric pressures, whereas change in lung volume appear to minimally influence CO.\(^{81}\) On the other hand, O’Donnell et al.\(^{54}\) have suggested that respiratory muscle work per se is not a major determinant of dyspnea in heart failure patients, but, rather, their respiratory discomfort may originate in the expiratory flow limitation and hyperinflation these patients experience during even moderate-intensity exercise.

**Summary and conclusions**

Lung and chest wall are highly efficient for long duration of exercise at high intensity. The following evidences support this conclusion:

1. sufficient dynamic capacity of generating pleural pressure to meet or sustain ventilatory requirements.
2. total \( \text{VO}_2 \text{cost of hyperpnea (VO}_2 \text{resp}) \) less than 10% \( \text{VO}_2 \text{max}. \)
3. respiratory muscle fatigue does not compromise an adequate alveolar ventilation.
4. work and cost of breathing of primary and accessory respiratory muscles may compete with locomotor muscles to blood flow supply and \( \text{O}_2 \) uptake in healthy subjects only during very heavy exercise.

On the other hand, abnormality of \( \text{O}_2 \) transport and utilization may contribute to depressing \( \text{VO}_2 \text{max} \) in patients with COPD. How much of the abnormal peripheral skeletal muscle oxidative metabolism is related to inadequate \( \text{O}_2 \) delivery in these patients remains to be defined.

Last but not the least, can these muscle limitations be overcome? Specifically, what is the role of respiratory muscle training (RMT) on the limitation on exercise performance imposed by the respiratory muscles? Has specific RMT the potential to increase exercise performance by means of delaying fatigue of the diaphragm and its associated vasoconstrictor influences, and reducing diaphragmatic sensations during high intensity exercise? Studies are needed to answer these questions.

**References**


